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Original article

Left ventricular end-diastolic pressure and ejection fraction correlate independently with high-sensitivity cardiac troponin-T concentrations in stable heart failure

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ABSTRACT

Background: Cardiac troponin is widely accepted as a biomarker of myocyte injury in patients with myocardial ischemia. Patients with congestive heart failure are also associated with elevated cardiac troponin and it is a very sensitive prognostic marker. However, the mechanisms of troponin elevation in patients with heart failure are not fully understood. Decompensated state itself is suggested as a factor contributing to elevated cardiac troponin-T. However comparison between invasive hemodynamic parameters and cardiac troponin-T is insufficient.

Methods: Data were collected from 167 patients in stable, chronic HF, without acute coronary syndrome, recent revascularization, mitral stenoses, hemodialysis, or clinically significant right HF. We evaluated the correlations and 95% confidence intervals (CI) between invasive hemodynamic measurements and serum high-sensitivity (hs) concentrations of cTnT.

Results: The serum cTnT concentration was equal to or more than the detection threshold (0.003 ng/ml) in all patients. The serum cTnT concentration was equal to or more than the cut-off value of 0.014 ng/ml in 46% of patients. By multiple variable analysis, left ventricular (LV) end-diastolic pressure (EDP; adjusted coefficient = 0.014; 95% CI 0.0003–0.029; $P = 0.046$) was positively correlated, while hemoglobin (adjusted coefficient = −0.079; 95% CI −0.140 to −0.018; $P = 0.012$), estimated glomerular filtration rate (adjusted coefficient = −0.008; 95% CI −0.013 to −0.003; $P = 0.004$), and LV ejection fraction (EF; adjusted coefficient = −0.011; 95% CI −0.018 to −0.003; $P = 0.004$) were negatively correlated with hs-cTnT concentrations.

Conclusion: In patients with stable chronic HF, LVEDP and LVEF correlate with the serum concentrations of hs-cTnT, independently of other correlates of elevated plasma concentrations of hs-cTnT.

Introduction

The serum concentration of cardiac troponin (cTn) is a widely used biomarker of myocyte injury in patients with myocardial ischemia, and a sensitive indicator for the early diagnosis and risk stratification of acute coronary syndrome [1]. cTn I and T are also elevated in patients with congestive heart failure (HF) without overt ischemia [2], representing a highly sensitive prognostic marker of HF progression [3,4], though the mechanisms of cTn elevation in this context are not completely understood. One hypothesis is that cardiac decompensation itself causes a continuous loss of cardiomyocytes and leak of cTn. In support of this hypothesis, Horwich et al. [5] and Eggers et al. [6] found an association between serum cTn concentrations and pulmonary capillary wedge pressure (PCWP), suggesting that the abnormal hemodynamics status contributes to the elevated cTn in patients with HF. This hypothesis, however, has not been confirmed by comparisons between cTn concentrations and direct invasive measurements of left ventricular (LV) end-diastolic pressure (EDP), particularly in peripheral blood sampling.

The primary objective of this study was to evaluate the correlation between invasive measurements of left heart hemodynamic function, and high sensitivity (hs) cTnT in patients with stable chronic HF of various etiologies.

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Methods

Study population

Data were retrospectively collected in 167 consecutive patients presenting with chronic and stable HF, who underwent complete right and left heart catheterization within one week from troponin measurement. Coronary angiograms were concurrently performed in all patients and patients with angiographically visible, high-grade coronary stenosis were excluded. Patients presenting with acute HF, acute coronary syndrome, coronary revascularization in the last 6 months, mitral stenosis, clinically significant right HF, or patients undergoing hemodialysis were also excluded from the study. This study complied with the principles outlined in the Declaration of Helsinki. The authors had full access to and take responsibility for the integrity of the data.

Hs-cTnT measurements

Serum hs-cTnT was measured from the blood sampling which was collected from the vein of the arm, using the Elecsys 2010® assay (Roche Diagnostics, Tokyo, Japan). The detection threshold of this assay is 0.003 ng/ml, while the 99th percentile of the upper reference value for healthy subjects is 0.014 ng/ml.

Baseline characteristics of the study sample

The baseline characteristics and medication status were obtained from patient interviews or reviews of their medical records. Body mass index was calculated from the individual's body weight, expressed in kg, divided by the square of height, expressed in meters. Ischemic heart disease was defined as a history of coronary revascularization, a significant coronary stenosis on angiography or positive result of stress tastings. Patients with a fasting serum glucose $\geq$ 126 mg/dl, a non-fasting serum glucose $>$ 200 mg/dl, or treated with an anti-diabetic medication were classified as diabetics. Hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg, a diastolic blood pressure $\geq$ 90 mmHg, or the use of an anti-hypertensive medication.

Hemodynamic measurements

Right heart catheterization was performed with a 7 or 5-French Swan-Ganz catheter (Edwards Lifesciences, Tokyo, Japan) inserted under local anesthesia from the femoral, brachial or jugular approach. Mean right atrial pressure, mean pulmonary artery pressure, and PCWP were measured at the end of expiration. Cardiac output and cardiac index were measured by the thermodilution method. Left ventriculograms were performed with a 5 or 4-French pigtail catheter inserted into the left ventricle from the femoral, brachial or radial approach. Mean aortic pressure, LVEDP, LV ejection fraction (EF) and LV end-diastolic volume were calculated from the measurements made during left heart catheterization. Coronary angiograms were performed in all patients.

Statistical analyses

The results are presented as means $\pm$ standard deviation (SD) or medians and interquartile range (IQR), as appropriate. The patient population was divided into 2 groups based on the baseline hs-cTnT concentration, using a cut-off value of 0.014 ng/ml, based on the 99th percentile of the upper reference value for healthy subjects, as mentioned earlier. Differences between the 2 groups were examined with Fisher's exact test or Wilcoxon rank-sum test, as appropriate. Single and multiple variable, linear regression analyses were performed to examine the correlations between serum cTnT concentrations and selected clinical, laboratory and hemodynamic variables. We used the log-transformed hs-cTnT concentration because of its positively skewed distribution. Variables emerging with correlations at the $P < 0.20$ level in the single variable analysis were entered in a stepwise regression model.

P value <0.05 was considered statistically significant. The statistical analyses were performed with the JMP® software version 9.0 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

We collected data from a total of 167 chronic heart failure patients. The etiology of HF was an old myocardial infarction in 84 patients (50%), valvular heart disease in 28 (17%), hypertensive heart disease in 26 (16%), dilated cardiomyopathy in 22 (13%) and arrhythmia-induced in 7 (4%) patients. Troponin measurement to the hemodynamic study was an average of 2.3 ($\pm$2.0) days. The serum hs-cTnT concentrations were equal to or more than the detection threshold (0.003 ng/ml) in all patients, and equal to or more than the selected cut-off value of 0.014 ng/ml in 77 patients (46%). The median hs-cTnT concentration was 0.012 ng/ml (IQR 0.007–0.022 ng/ml; Fig. 1).

Relationships between hs-cTnT and baseline patient characteristics and laboratory data

The relationships between hs-cTnT and selected baseline characteristics and laboratory measurements are shown in Table 1.

Hemodynamic measurements in patients with normal versus elevated serum hs-cTnT concentrations

The hemodynamic measurements made in patients with versus without elevation of serum cTnT concentrations are shown in Table 2. Compared with patients whose hs-cTnT was $\leq$0.014 ng/ml, patients whose hs-cTnT was above the cut-off concentration had significantly lower mean LVEF, and higher mean right atrial pressure, pulmonary artery pressure, PCWP, and LVEDP. Mean heart rate, cardiac index, LV end-diastolic volume index, and mean aortic pressure were similar in both groups.

Outcomes of single and multiple variable regression analyses

By single variable analysis, age, female sex, mean pulmonary artery pressure, PCWP, and LVEDP were positively correlated, while serum hemoglobin, eGFR, and LVEF were negatively

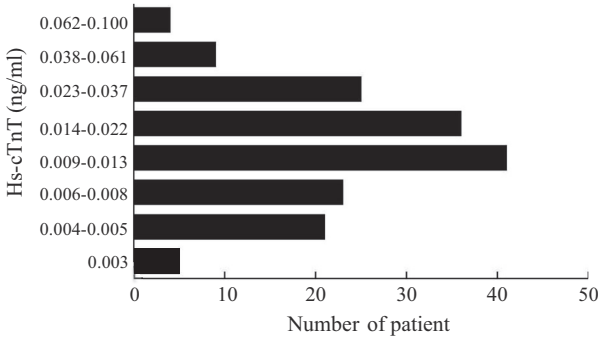

Fig. 1. Distribution of cTnT in the overall study population. See text for further explanations. Hs-cTnT, high sensitive cardiac troponin

Table 1
Comparisons of the baseline characteristics of patients with serum cTnT concentrations ≤0.014 versus >0.014 ng/ml cut-off value.

	cTnT ≤0.014 ng/ml (*n* = 90)	cTnT >0.014 ng/ml (*n* = 77)	*P*
Age (years)	69.3 ± 11	72.0 ± 11	0.080
Men	57 (63)	41 (53)	0.209
Body mass index (kg/m^2)	23.3 [20.9–25.5]	23.7 [19.7–25.9]	0.560
Ischemic etiology	51 (57)	35 (45)	0.164
Hypertension	71 (79)	57 (74)	0.470
Diabetes	35 (39)	22 (29)	0.191
Hemoglobin (g/dl)	13.0 ± 1.7	12.5 ± 1.9	0.042
Estimated glomerular filtration rate (ml/min/1.73 m^2)	69.5 ± 21	59.6 ± 18	0.003
Hemoglobin A1c	5.83 ± 0.81	5.89 ± 1.14	0.670
Drug therapy			
Renin-aldosterone-angiotensin antagonist	57 (63)	50 (65)	0.872
Beta-adrenergic blocker	70 (78)	53 (69)	0.219
Diuretic	32 (36)	48 (63)	<0.001

Values are means ± SD, numbers (%) of observations or medians [interquartile range]. cTnT, cardiac troponin T.

Table 2
Hemodynamic measurements and serum cTnT concentrations.

	cTnT ≤0.014 ng/ml (*n* = 90)	cTnT >0.014 ng/ml (*n* = 77)	*P*
Heart rate (bpm)	69.1 ± 16	71.2 ± 14	0.368
Central pressures (mmHg)			
Mean right atrial	5.7 ± 2.4	6.8 ± 3.5	0.049
Mean pulmonary artery	18.7 ± 5.3	22.3 ± 8.0	0.003
Pulmonary capillary wedge	10.9 ± 4.5	14.3 ± 7.0	0.002
Left ventricular end-diastolic	13.5 ± 6.1	16.9 ± 8.4	0.010
Mean aortic	97 ± 16	96 ± 17	0.699
Cardiac index (l/min)	3.3 ± 0.8	3.1 ± 0.8	0.082
Left ventricular			
End diastolic volume index (ml/m^2)	93 ± 27	101 ± 35	0.205
Ejection fraction (%)	50.1 ± 12.8	44.9 ± 15	0.048

Values are means ± SD. cTnT, cardiac troponin T.

correlated with hs-cTnT (Table 3). By multiple variable analysis, LVEDP was independently and positively correlated, while hemoglobin, eGFR, and LVEF were independently and negatively correlated with hs-cTnT. Because PCWP shows a good correlation with LVEDP in general, they may be potential confounding variables in multivariable analysis. However, in this study after we excluded PCWP from a multivariable analysis, the result did not change. In Fig. 2 the values of LVEDP, LVEF, hemoglobin and eGFR are shown in 3 groups of different troponin levels (Group1: Log TnT < −4.71, *n* = 56; Group2: −4.71 ≤ Log TnT < −4.017, *n* = 57; Group3: −4.017 ≤ Log TnT, *n* = 54).

Discussion

Our study of patients presenting with stable HF found significant relationships between serum concentrations of hs-cTnT and anemia, renal insufficiency, depressed LVEF and elevated LVEDP.

Anemia and cTnT

About patients with heart failure, Ralli et al. had shown the relationship between anemia and troponin concentration [7]. We confirmed the independent and linear correlation between hemoglobin and serum hs-cTnT concentrations. The correlation between hemoglobin and hs-cTnT was strong and independent from other predictors of elevated hs-cTnT, such as renal insufficiency. Anemia is common in presence of chronic inflammatory diseases, and some markers of inflammation are also positively correlated with the serum concentrations of cTnT [2,8]. Although in this study we did not investigate relationships between anemia and inflammation, anemia concomitant with inflammation may cause further elevation of cTnT in heart failure than anemia alone.

Left ventricular function and cTnT

In this study LVEF was correlated with hs-cTnT concentrations measured using the Elecsys 2010® assay (Roche Diagnostics, Tokyo, Japan), however in our previous study LVEF was not correlated with cTnI concentrations measured using rapid assay PATHFAST (Mitsubishi Chemical, Tokyo, Japan) in patients undergoing cardiac catheterization [9]. Although cTnT and cTnI are both expressed in cardiomyocytes, it has been reported that the

Table 3
Outcomes of single and multiple variable regression analyses.

	Unadjusted					Adjusted				
	Coefficient	SE	95% CI		*P*	Coefficient	SE	95% CI		*P*
Age (years)	0.010	0.005	0.0003	0.020	0.044					
Sex (*m* = 1)	−0.248	0.115	−0.474	−0.021	0.032					
Body mass index (kg/m^2)	−0.012	0.014	−0.040	0.016	0.396					
Hemoglobin (g/dl)	−0.102	0.031	−0.015	−0.004	0.001	−0.079	0.031	−0.140	−0.018	0.012
Estimated GFR (ml/min/1.72 m^2)	−0.010	0.003	−0.015	−0.004	<0.001	−0.008	0.003	−0.013	−0.003	0.004
Glycated hemoglobin A1c (%)	0.047	0.059	−0.069	0.163	0.421					
Heart rate (/min)	0.001	0.004	−0.006	0.008	0.806					
Central pressures (mmHg)										
Mean right atrial pressure	0.017	0.019	−0.020	0.054	0.361					
Mean pulmonary artery pressure	0.017	0.008	0.0004	0.033	0.045					
Pulmonary capillary wedge pressure	0.022	0.009	0.003	0.040	0.021					
LV end-diastolic pressure	0.019	0.008	0.004	0.034	0.011	0.014	0.007	0.0003	0.029	0.046
Mean aortic pressure	−0.003	0.003	−0.009	0.004	0.451					
Cardiac index (l/min/m^2)	−0.108	0.071	−0.248	0.031	0.127					
LV end-diastolic volume index (ml/m^2)	0.003	0.002	−0.0001	0.007	0.054					
LV ejection fraction (%)	−0.009	0.004	−0.017	−0.001	0.032	−0.011	0.004	−0.018	−0.003	0.004

SE, standard error; CI, confidence interval; GFR, glomerular filtration rate; LV, left ventricular.

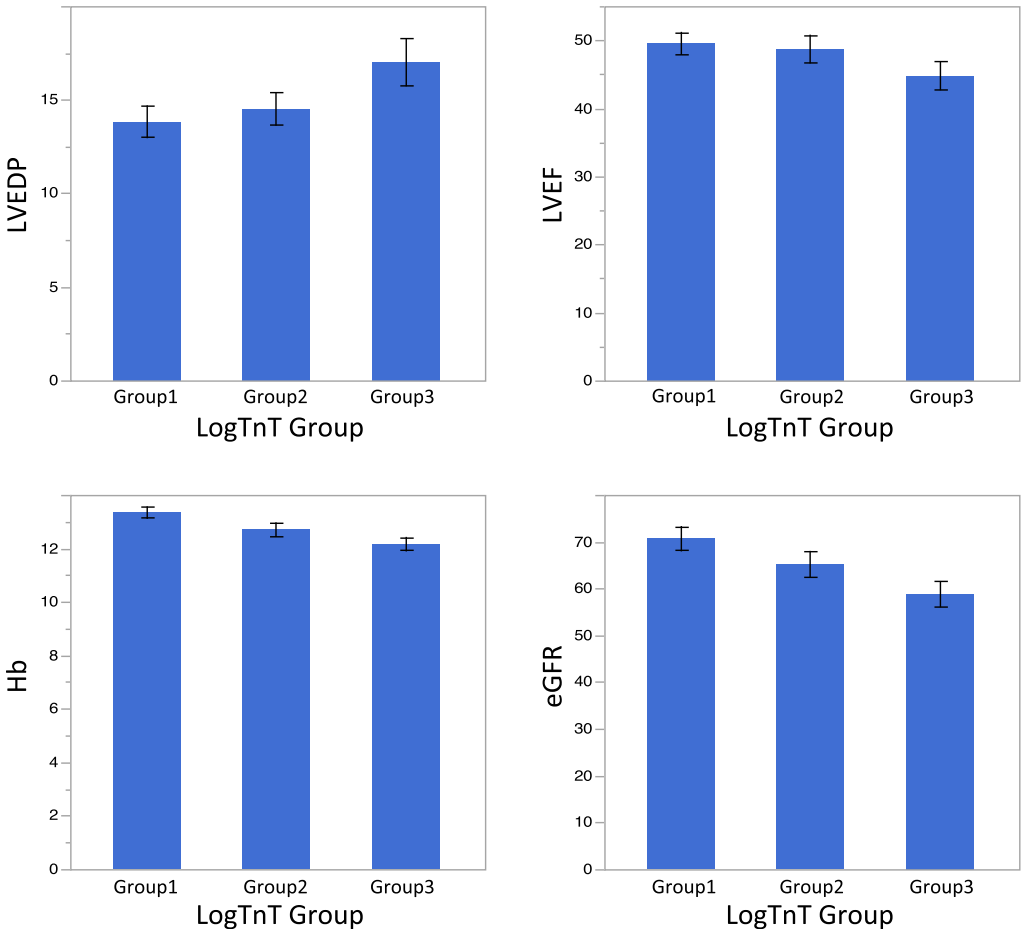

Fig. 2. The values of LVEDP, LVEF, hemoglobin and eGFR in 3 groups of different troponin levels (values are means ± SE). See text for further explanations.

detectivity of cTnI is different from cTnT under various conditions such as male gender or renal failure, which may be due to epitopic differences that are detected by individual assays and by the degradation of troponin [10]. These differences in cTn may have influenced our findings. The relationship between LVEF and cTnT concentrations has been reported in other previous studies [4,11–13]. Earlier studies in patients with chronic HF have shown specific relationships between elevated cTn and cardiac load [5,6], activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, and inflammation [2]. cTn is also a reliable marker of LV remodeling [14–16]. In this study, LVEF was an independent correlate of hs-cTnT, suggesting that its elevation reflected a myocytic injury and LV remodeling secondary to pathways that we did not identify.

Renal insufficiency increases the serum concentrations of cardiac troponin

We observed a correlation between impaired renal function and elevated hs-cTnT. Although the relationship between renal function and cTn remains controversial, several previous studies have found higher hs-cTnT concentrations in patients presenting with chronic HF and chronic kidney disease than in patients without renal insufficiency [17,18]. Earlier observations revealed that fragments of cTnT are not properly excreted by malfunctioning kidneys and remain in the plasma [19]. The results of our study are concordant with these previous observations.

Left ventricular end-diastolic pressure and serum troponin concentrations

The relationships between hemodynamic measurements and cTn have been described in the studies by Horwich et al. [5] and Eggers et al. [6]. Ours found a linear relationship between hs-cTnT and LVEDP, which is the most reliable indicator of LV filling pressure. Takashio et al. reported the differences between coronary sinus (CS) and aortic root (Ao) cTnT levels correlate with LVEDP [20]. However, because measurement of CS and Ao cTnT is difficult in real-world clinical practice, we investigated the relationships between cTnT concentrations in peripheral blood sampling and hemodynamic measurements. Our data support the hypothesis that cardiac decompensation is associated with myocyte injury and disease progression [21]. The association of elevated LVEDP with elevated hs-cTnT remains unexplained. One hypothesis is that high LV filling pressures cause myocyte injury by interfering with endomyocardial perfusion [21]. Another experimentally supported hypothesis is the release of cTn caused by myocytic stretch [22].

Limitations of our study

To the best of our knowledge, this is the first report showing a correlation of LVEDP measured directly and LVEF calculated from the measurements made during left heart catheterization with hs-cTnT concentrations in peripheral blood sampling. Although we know that cTnT released from falling myocardium correlate with

microvascular dysfunction in nonischemic HF patients [20], we do not have data about it in this study. Furthermore, the results of our study are limited by a relatively small patient sample and the observational study design. Whether controlling LVEDP has an impact on the serum concentrations of cTn and on prognosis warrants further investigations.

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Conflict of interest

The authors have no potential conflict of interest to disclose.

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